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EXAMINER	
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ART UNIT	PAPER NUMBER
1613	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/056,348	BURCH ET AL.	
	Examiner	Art Unit	
	Jennifer A. Berrios	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 47-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/5/2010 and 4/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the reply filed 3/24/2010 wherein claims 1-37 and 39-46 have been cancelled and claims 68-73 have been newly added.

Currently claims 38 and 47-73 are being examined.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Jennifer A. Berríos in Art Unit 1613.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/2010 has been entered.

2. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information Disclosure Statement

3. The information disclosure statement filed 4/5/2010 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Maintained/Modified Rejections

4. Claims **38**, **47**, **48**, **50-52**, **62**, **63**, **66** and **68-69** as amended or originally filed are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47, 48, 50-52, 62-63 and 66 is

maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claim 68-69 is necessitated by applicant's amendment to the claims. (Claims 68-69 recite limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

Baker et al. teach pharmaceutical compositions for relieving pain in humans or mammals (e.g. mice, rats etc.) comprising a combination of:

a.) a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; mice data in col. 8-10; patent claims), or a pharmaceutically acceptable salt thereof (reads on the salt of **clm 48**); and

b.) ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof,

in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present **claims 47** and **63**: See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present **claims 46** and **52**).

The Baker reference also teaches various dosage formulations such as the ones listed on column 4 (e.g. Examples 1-4), which tablet formulation "consists" of an oxycodone salt, Ibuprofen, and "at least one pharmaceutically acceptable excipient" including "microcrystalline cellulose", "starch", and "stearic acid". These formulations read on the oral dosage form of the instant **claim 38** except Ibuprofen is included instead of nabumetone. As recited in the various Examples (col.4), the amount of Ibuprofen (a NSAID compound) ranges from 60-300 mg, which range reads on the range recited in **claim 51, 68-69**. For example daily dosages range from 10-120 mg/kg of ibuprfen (Col. 3, lines 55-56), which reads on instant claim **68-69**.

The dosage formulation of Baker also inherently teaches inclusion of oxycodone and at least one salt thereof as recited in **claim 62**, because it is an inherent property of the oxycodone

salt (such as Oxycodone HCl) to comprise the Oxycodone compound itself. Thus, the formulation of the Baker reference comprises Oxycodone and at least a salt thereof.

The Baker reference further teaches oral administration (reads on the instant oral dosage form of **claim 38**), which can be co-administered in a single dosage form (e.g. see col. 3-8) or sequentially administered (e.g. see i.e. col. 8-9; mice are dosed sequentially...). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4), which reads on the sustained release formulations of **claim 50**. The Baker et al. reference also teaches that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is unexpectedly enhanced or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32). Accordingly, Baker would teach the use of therapeutic and sub-therapeutic amounts of oxycodone and/or ibuprofen in view of the synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient., including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

The Baker reference does not explicitly teach an oral analgesic composition comprising nabumetone instead of ibuprofen. The Baker reference also does not explicitly teach an oral dosage formulation comprising of nabumetone and at least one salt thereof as recited in the instant claims.

However, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claims 51** and **66**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to substitute nabumetone and/or pharmaceutical acceptable salt thereof (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Friedel and/or Eversmeyer reference

teachings that nabumetone is equally efficacious, but is safer with less side effects (e.g. as compared to ibuprofen).

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting the NSAID nabumetone with the appropriate amount (and/or pharmaceutical acceptable salt thereof) for the NSAID ibuprofen in light of the benefits of nabumetone (increased safety/decreased side effect as compared to ibuprofen) as taught by the Friedel and/or Eversmeyer reference references, to achieve the predictable result of formulating an analgesic oral dosage form for pain treatment. In addition, making and using compounds such as nabumetone and/or pharmaceutical acceptable salt thereof (as part of a combination drug) is routine and known in the art as taught by the cited references.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all cited references have demonstrate the success of making various pharmaceutical formulations comprising various analgesic compounds including oxycodone and nabumetone as well as various pharmaceutical acceptable excipients.

Response to Arguments

Applicants argue that the combination of the cited references does not teach or suggest administering nabumetone together with oxycodone, e.g., because the Friedel and Eversmeyer articles describe administration of nabumetone by itself, without any additional analgesic agents. Applicants further submit that there is nothing in the cited references to suggest that

administration of nabumetone by itself will not produce adequate analgesia. Accordingly, Applicants submit that the combination of the cited references does not teach or suggest administration of nabumetone in combination with oxycodone as recited in claim 38.

This is not persuasive. Although the references of Friedel and Eversmeyer demonstrate the use of nabumetone by itself, these references are simply cited to teach the pharmacokinetic properties of Nabumetone and demonstrate that nabumetone and ibuprofen are functional equivalents. The primary reference, Baker, is cited to demonstrate the combination of Oxydodone and ibuprofen and as ibuprofen and nambutone are functional equivalents (both function as NSAIDs) as demonstrated by the teachings of Friedel and Eversmeyer, it would be obvious to one of skill in the art to substitute one for the other, with reasonable expectation of success, absent evidence to the contrary. Furthermore, Friedel and Eversmeyer teach that nabumetone demonstrates fewer side effects that other NSAIDs.

Applicant further argues "In response to the Examiner's reliance on the case law on pages 14 and 17 of the Office Action, Applicants respectfully note that the claims at issue in the relied upon cases were not directed to a method of treating pain in a human patient, and that the Examiner's reliance on these cases may therefore be inappropriate."

This is not persuasive. The case law cited (MPEP 2143.02) states "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." The claims at issue of the case are a demonstration of an example and are not intended to limit the case law to claim pertaining only to methods of treating depressions. As long as the Examiner is able to demonstrate a reasonable expectation of success, the obviousness rejection is proper. Furthermore, applicant has not demonstrated any factual evidence demonstrating that the reasonable expectation of success presented in the rejection above would not result in a functional composition.

Applicant further argues that the combination of the cited references does not provide a reason for combining nabumetone with a pharmaceutically acceptable excipients "which provides a sustained release of nabumetone" as recited in claim 50, e.g., because the Friedel article describes a mean elimination half-life of, e.g., 38.8 and 26.3 hours, after administration of a single dose of 1 g of nabumetone.

This is not persuasive. Baker teaches sustained release formulations of oxycodone and a NSAID compound, thereby satisfying the limitation of claim 50. Furthermore, applicant hasn't provided any actual evidence demonstrating that the nabumetone of Friedel combined with the Baker reference would not result in a functional sustained release composition.

Applicant further argues that the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, e.g., because the Friedel and Eversmeyer articles describes administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg).

While Friedel and Eversmeyer teach higher ranges of nabumetone, Baker teaches the use of NSAIDs compounds, such as ibuprofen, in amounts ranging from 10-120 mg/kg and 60-300mg, as taught in the above rejeciton. Based on the teachings of Baker, Friedel and Eversmeyer one of skill in the art is aware that nabumetone and ibuprofen are equally efficacious NSAID compounds, which can be substituted for one another, therefore, nabumetone can be used in the composition of Baker in the quantities taught by Baker to be appropriate for NSAID compounds.

5. Claims **38**, **47-67** and **70-73** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baker** et al., (US Patent 4,569,937; 2/11/1986; cited previously), **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of

Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously) as applied to claims 38, 47, 48, 50-52, 62, 63, 66 and 68-69 above, and further in view of **Oshlack** et al. US Pat. No. 5,472,712 (12/95) or **Oshlack** et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier). The previous rejection over claims 38 and 47-65 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 70-73 is necessitated by applicant's amendment to the claims. (Claims 70-73 recite limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

The substance of the above obviousness rejection (the rejection over the combination of Baker, Friedel and Eversmeyer) is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms which include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference does not explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or ... salt thereof" and "a sustained release of the nabumetone..." as recited in the instant claims 49, 59, 64, 65 etc. The Baker reference also does not explicitly teach using "an immediate release form" for nabumetone in the formulation (as recited in the instant claim 53) as well as formulation comprising particles of 0.5 to 2.5 mm in diameters as recited in the instant claims 57 and 58.

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone such as utilizing sustained release carriers, beads (or particles with various diameters) as well as using immediate release formulation for non-opioid drugs in a combination drug formulation are known and routine in the art. Using beads/particles coated with the opioid drug including substrate layers which comprise the drugs is also known in the art to produce

delayed release of extended duration. For examples, **Oslack** et al ('712 patent) teach drug formulation of sustained (or controlled) release formulation of various compounds including the controlled release of oxycodone (e.g. col.14, lines 15+); Oslack et al ('195 patent) also teach sustained oral formulation for opioid analgesics (e.g. Abstract) including oxycodone (e.g. col.6, lines 30+). The Oslack ('195) patent specifically teach using particles with diameters of about 0.1mm to about 3 mm (e.g. Abstract), which reads on the particles of **clms 57** and **58**. The Oslack ('195) patent also teaches using "immediate release" formulation for "a second (non-opioid) drug", incorporated into immediate release layer, or coating, etc. (e.g. col.7, lines 21+), which reads on the immediate release formulation of **clm 53** and the coating layer of **clm 59**. The Oslack ('195) reference also teaches incorporating sustained release matrix with the opioid drug (e.g. col.11, lines 30+), which reads on the sustained carrier of **clm 60**. The Oslack ('195) reference also teaches various sustained release carrier such as "hydroxyalkylcellulose" (e.g. col.11, lines 34+), which reads on the sustained carrier of **clm 55**. The Oslack ('195) reference also teaches the sustained release formulations provide about at least 12 hour or about 24 hours, or longer release time for opioid drugs (e.g. col.5, lines 40+), which reads on the release time of **clms 54** and **61**. The Oslack ('195) reference also teaches treating pain for cancer patients (e.g. col.1, lines 50+), which the cancer pain reads on the types of pains listed in **clm 56**. Both of the references also teach the advantages of sustained release formulation. For example, the '195 patent teaches the controlled or sustained release oral dosage formulation would provide effective blood levels of the opioid analgesic for at least about 24 hours (e.g. Abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize various known and routine formulations to make various analgesic compositions that have various release rates. For examples, the sustained release carriers for

oxycodone including beads/layers as well as the immediate release formulations for the other non-opioid drug in the same formulation as taught by the Oshlack and Oshlack et al. patents. A person of ordinary skill in the art would have been motivated at the time of the invention to use the various formulations as disclosed in Oshlack references (i.e. the various time releasing formulations) to make a combination drug based on a sustained releasing opioid drug (such as oxycodone) and an immediate releasing non-opioid drug (such as nabumetone), because Baker et al and Oshlack ('195) patent specifically teach "sustained release formulations" for the opioid drug is known and routine, and the advantages of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration especially for treatment of cancer pains. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of formulating sustained release formulation (especially for oral administering an opioid analgesic such as oxycodone) as taught by both the Oshlack patent references, to improve the delivery of the analgesic compounds for the predicable result of enabling standard pharmaceutical formulation and administering.

A person of ordinary skill in the art would have been motivated at the time of the invention to use immediate or sustained release formulation for the non-opioid drug (such as Nabumetone) in the same combination drug formulation, because Oshlack ('195) patent teaches the advantages of using immediate release formulation such as an "immediate releasing layer" to coat the opioid drug to afford differential drug release rates for efficient pain treatments. In addition, because all the cited references teach methods of making various combinations of drugs in the same pharmaceutical composition with various releasing matrices, coating, particles, etc., for various pain treatments, it would have been obvious to one skilled in the art to substitute one type of releasing formulation (such as sustained release) for the other (such as immediate release or combinations of sustained and immediate release formulations)

to achieve the predictable result of making pharmaceutical composition with optimized drug releasing rates.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of making and using various drug formulations (including sustained/immediate release formulations, coating, tablets, particle matrix, etc.) especially for various analgesic compounds.

Response to Arguments

Applicants argue that the combination of the cited references does not teach or suggest administering nabumetone together with oxycodone, e.g., because the Friedel and Eversmeyer articles describe administration of nabumetone by itself, without any additional analgesic agents. Applicants further submit that there is nothing in the cited references to suggest that administration of nabumetone by itself will not produce adequate analgesia. Accordingly, Applicants submit that the combination of the cited references does not teach or suggest administration of nabumetone in combination with oxycodone as recited in claim 38.

Applicant further argue that the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, e.g., because the Friedel and Eversmeyer articles describes administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg).

Examiner would like to direct applicant to the *Response to Arguments* section following the rejection over references Baker/Friedel and Eversmeyer, where these arguments have been previously addressed.

6. Claims **38, 47-52 and 62-66** are rejected under **35 U.S.C. 103(a)** as being unpatentable over **Mayer** et al (US 5,840,731; 11/24/1998; filed on 8/2/1995; cited previously), and if

necessary in view of **Friedel** et al (Drugs. 1993. Vol. 45 (1): 131-156; cited previously) and **Eversmeyer** et al., (American Journal of Medicine. Aug. 1993, Vol. 95: 10S-18S; cited previously). The previous rejection over claims 38, 47-52 and 62-65 is maintained for the reasons of record advanced in the previous office actions as well as for the reasons below. The rejection over claims 68-69 and 72-73 is necessitated by applicant's amendment to the claims. (Claim 68-69 and 72-73 recite limitations that are encompassed by the previously presented claim 51, and would have been rejected with the same references (as used for claim 51)).

Mayer et al, throughout the patent, teach methods of treating pain using various drug compositions (see Abstract; Claim 2), which reads on the claimed treatment method of **clms 38** and **62**.

The reference also teaches the compositions of drugs can be combinations of drugs (e.g. col.1, lines 24+), and especially combination between Opioid analgesics and NSAIDS (e.g. col.1, lines 50+). The reference also teaches "the first component of the drug composition" is an opioid such as "oxycodone" and/or their pharmaceutically acceptable salts (e.g. col.3, lines 57+). The reference also teaches "the second component of the drug composition" is "of the nonopioid type… of any of the foregoing" (col.4, lines 11+), and the reference discloses the nonopioid analgesics includes "nabumetone" and/or its pharmaceutically acceptable salts (col.3-4; bridging). These passages of the reference teach a composition for pain treatment comprising oxycodone and nabumetone of **clms 38** and **62.**

The reference also teaches pharmaceutical acceptable carriers (e.g. col. 5), which reads on the component of **clms 38**, **48** and **62.** The reference also teaches, for example, 4.5 mg of oxycodone (see Table in between cols. 5-6), which reads on the dosage amount of **clm 52**.

The reference also teaches various amounts of the "first" and "second" components of the drug (e.g. col.5-6; Examples), which read on the ratios recited in **clms 47** and **63**.

The reference also teaches using various drug formulations such as gelatin capsules (e.g. col.5, lines 5+), which reads on the sustained release carriers of **clms 49**, **50**, **64** and **65**.

The Mayer reference does not explicitly teach using "an oral dosage form consisting of (i) nabumetone… (ii) oxycodone… and (iii) at least one pharmaceutically acceptable excipient" as recited in **clms 38** and **62**.

However, the Mayer reference teaches a number of drug combinations for alleviating pain… are known" (e.g. col.1, lines 24+). As discussed supra, the Mayer reference also teaches combination of an opioid drug such as oxycodone and a NSAID drug such as nabumetone is known in the prior art to be effective analgesic (e.g. cols.3-4). In addition, the Mayer reference also teaches the necessary ingredient of pharmaceutically acceptable excipient as part of a pharmaceutical composition (e.g. col.5).

In addition, **Friedel** et al. teach that nabumetone (and/or pharmaceutical acceptable salt thereof) possesses the typical pharmacodynamic properties of the nonsteroidal class of anti-inflammatory (NSAID) drugs including intrinsic analgesic and antipyretic activity being demonstrated in animal studies and in humans with the following advantages over other NSAIDS:

a. does not exert a significant direct toxic effect on the gastric mucosa during absorption;

b. in studies, produced a lower incidence of gastrointestinal erosions or microbleeding than aspirin, naproxen, piroxicam and ibuprofen; and

c. more recently clinical data further confirmed the efficacy and tolerability of nabumetone ; "Thus, the drug (e.g. nabumetone and/or pharmaceutical acceptable salt thereof) should now be considered a well established member of this group of agents (e.g. NSAIDS) for the treatment of painful rheumatic and inflammatory conditions". See e.g. Abstract, pages 132-133 as well as the remainder of Friedel.

In addition, the Friedel reference also teaches various dosage amounts (such as 1000 mg-1500 mg) of nabumetone can be used for various treatment depending on the severity of the symptoms (e.g. p.133, bottom), which reads on the amount of nabumetone as recited in **claim 51**.

Similarly, **Eversmeyer** et al. teach that nabumetone is equally efficacious in the treatment of arthritic pain patients (e.g. osteo/rheumatoid arthritis) but has shown to be more safe, with reduced side-effects (e.g. dyspepsia, ulcers, reduced hemoglobin, gastritis etc.). See Eversmeyer et al. Abstract and disclosed studies.

Accordingly, one of ordinary skill in the art would have been motivated to combine nabumetone (a NSAID) and/or pharmaceutical acceptable salt thereof with Oxycodone (an opioid analgesic) in light of the Mayer, the Friedel and/or Eversmeyer reference teachings that nabumetone is equally efficacious, but is safer with less side effects.

Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to make and use an oral dosage form consisting of only oxycodone and nabumetone with at least one pharmaceutically acceptable excipient.

A person of ordinary skill in the art would have been motivated at the time of the invention to make and use an oral dosage form consisting of only oxycodone and nabumetone (with an appropriate amount) with at least one pharmaceutically acceptable excipient, because dosage forms of combinations of analgesic drugs (such as oxycodone and nabumetone) are routine and known in the art. In addition, the Mayer reference teaches the advantages of making

and using pharmaceutical composition comprising a combination of an opioid drug and a NSAID drug so that a synergistic effect can be achieved. Further, the Friedel and/or Eversmeyer references teach the advantages of Nabumetone. Because the Mayer reference teach methods of making and using various drug formulation comprising different combinations of an opioid drug and a NSAID drug, it would have been obvious to one skilled in the art to substitute one drug for the other to achieve the predictable result of making and using routine analgesic pharmaceutical composition. It would have been obvious to one of ordinary skill in the art to apply the standard technique of adding at least one "pharmaceutically acceptable excipients" as taught by Mayer et al, to improve pharmaceutical formulation for the predicable result of enabling standard making and using a pharmaceutical composition for treatment of pain.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since Mayer et al have demonstrated the success of generating and using various pharmaceutical formulations.

Response to Arguments

Applicants argue that a dosage form in accordance with the Mayer patent will necessarily include "a nontoxic N-methyl-D-aspartate receptor antagonist," e.g., because the Mayer patent states that "the analgesic effectiveness of known combination drugs containing at least one analgesic drug can be significantly enhanced by the addition of a nontoxic N-methyl-D-aspartate receptor antagonist.". Applicants therefore submit that the Mayer patent (alone or in combination with the Friedel and Eversmeyer articles) does not therefore provide a reason for the skilled person to formulate a dosage form without "a nontoxic N-methyl-D-aspartate receptor antagonist."

Applicant further argues that "A nontoxic N-methyl-D-aspartate receptor antagonist" is excluded from the scope of the rejected claims, by virtue of the "consisting of' language recited

in independent claims 38 and 62. These claims are not therefore rendered obvious by the combination of the cited references, because the mandatory ingredient of the primary reference (i.e., "a nontoxic N-methyl-D-aspartate receptor antagonist") is excluded from the scope of the rejected claims.

This is not persuasive. As applicant have stated above the Mayer patent teaches that a nontoxic receptor antagonist **can** be added to a known combination of drugs in order to make that known combination of drugs more effective. As the receptor antagonist **can** be added, it is an optional ingredient and can be in fact be excluded. Furthermore, Mayer does not teach that a combination of drugs excluding the receptor antagonist would not perform its intended function of alleviating pain.

Applicant further argue that the combination of the cited references does not teach or suggest administering "from 25 mg to 300 mg of nabumetone" or "100 mg of nabumetone" as recited in these claims, e.g., because the Friedel and Eversmeyer articles describes administration of much higher doses of nabumetone (e.g., 500 mg to 2000 mg of nabumetone).

This is not persuasive, as applicant is arguing limitations that are not in the claims that were rejected over the Mayer reference. It is noted that claims 68-69 and 72-73 were not rejected above.

Conclusion

No claims are allowable.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer A. Berríos whose telephone number is (571)270-7679. The examiner can normally be reached on Monday-Thursday: 7:00am-4:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on (571) 272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer A Berríos/
Examiner, Art Unit 1613

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635